BLA: ***BLA 99-2672***
PEGASYS® (Interferon alpha-2a) for the treatment of chronic hepatitis C.
Hoffman-La Roche Inc.

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The clinical and statistical issues related to the review of this BLA have been discussed with the clinical staff from the Division of Clinical Trial Design and Analysis. This reviewer has analyzed the electronic data submitted by the sponsor. Results of our analyses are consistent with those given in the clinical report submitted by the sponsor. This review will summarize the observed results on the primary and key secondary efficacy endpoints.

This BLA submission included the safety and efficacy results from three randomized and controlled clinical studies summarized in the following sections.

I. Study NV15495

1. Design

This Phase II/III study was an *open-label*, randomized, and multicenter trial evaluating the safety and efficacy of 90 and 180 µg doses of PEG-IFN (administered once a week) in patients with chronic hepatitis C complicated by compensated cirrhosis or transition to cirrhosis. The patients in the control arm were given 3 MIU of IFN tiw. A total of 271 patients from 30 sites (from United States, Canada, Australia, and the United Kingdom) were randomized to the three arms. Randomization was centralized and was stratified by study center. Patients were treated for 48 weeks and then followed for an additional 24 weeks.

The primary efficacy parameter was a combined sustained virological and biochemical response at the end of the untreated follow-up period (i.e., at response at the end of 72 weeks). This rate was calculated as the number of patients with both a sustained biochemical and virological response divided by the number of patients randomized.

The secondary efficacy endpoints were sustained virological response at the end of follow-up, sustained biochemical response at the end of follow-up, and histological response in all patients and in patients with paired biopsies.

The sample size was estimated by assuming a combined sustained biochemical and virological response rate of 25% in the PEG-IFN groups, a 5% response in the IFN group, a power of 80%, and a two-sided significance level of 0.025. A dropout rate of 15% was also assumed for this estimation. Two pairwise comparisons (PEG-IFN 90 µg versus IFN and PEG-IFN 180 µg versus IFN) were to be made and, therefore, a significance level of 0.025 was used in all statistical testing.

2. Results

The response rates (primary and secondary efficacy endpoints) are given in Table 1.

The observed response rates in PEG-IFN 180 µg group were significantly (all P values <0.025) greater than those in IFN 3 MIU group. In PEG-IFN 90 µg group these rates were also higher than those in the IFN 3 MIU group but they were not statistically significant (P>0.025). Furthermore, there appears to be a dose response relationship in the effectiveness of PEG-IFN therapy with PEG-IFN 180 µg regimen superior to PEG-IFN 90 µg regimen for the primary and all the secondary parameters listed in Table 1.

Table 1. Study NV15495: Combined Sustained Biochemical and Virological Response at Week 72, Virological Response at Week 72, Biochemical Response at Week 72, and Histological Response at Week 72.

Response	Arm A IFN 3 MIU N=88 (%)	Arm B PEG-IFN 90 µg N=96 (%)	Arm C PEG-IFN 180 µg N=87 (%)	Odds Ratio (97.5% CI) A vs. B	Odds Ratio (97.5% CI) A vs. C
Sustained Response at Week 72					
Combined Virological and Biochemical	3	11	20	3.3 (0.7, 15.1) P=0.078	7.9 (2.0, 31.3) P=0. 001
Virological	5	13	28	2.6 (0.7, 10.1) P=0.120	8.1 (2.6, 25.2) P=0.001
Biochemical	7	15	23	2.2 (0.7, 7.4) P=0.142	4.7 (1.5, 15.0) P=0.003
Histological* (all patients)	19	28	43	1.4 (0.6, 3.2) P=0.314	2.8 (1.3, 6.4) P=0.004
Histological (in patients with paired biopsies#)	31	44	54	1.8 (0.6, 4.9) P=0.219	2.5 (1.1, 5.8) P=0.017

P-values are from Cochran-Mantel-Haenszel test stratified by center

* Histological response = decrease of at least 2 points in HAI score; patients without a liver biopsy at the end of untreated follow-up are
defined as nonresponders.

Patients with paired biopsies: N=55 in IFN 3 MIU; N=61 in PEG-IFN 90 ug; N=68 in PEG-IFN 180 ug.

II. Study NV15496

1. Design

This Phase III trial was a randomized, *open-label*, and multicenter study to evaluate the safety and efficacy of two doses of PEG-IFN in patients diagnosed with chronic hepatitis C. Patients who met the entry criteria were randomized to receive 135 µg or 180 µg of PEG-IFN once weekly or 3MIU of IFN tiw. All patients were treated for 48 weeks and then followed for an additional 24 weeks.

A total of 639 patients were enrolled and randomized at 52 centers from United States, Canada, Australia, France, and the United Kingdom. Randomization was centralized and was stratified by study center.

The primary efficacy parameter was a combined sustained virological and sustained biochemical response at the end of the 24 week untreated follow-up period. This rate was calculated as the number of patients with both a sustained biochemical and virological response divided by the number of patients randomized.

The secondary efficacy endpoints were sustained virological response at the end of follow-up, sustained biochemical response at the end of follow-up, and histological response in all patients and in patients with paired biopsies.

The trial was designed to demonstrate that the efficacy of PEG-IFN is superior to that of IFN. The study size was estimated by assuming a sustained response rate of 35% in either PEG-IFN group versus 20% in the IFN group, a power of 80%, a dropout rate of 15%, and an alpha level of 0.025 (to adjust for two pairwise comparisons).

2. Results

The results on the primary and secondary efficacy parameters are given in Table 2.

The combined sustained virological and biochemical response rates in PEG-IFN 135 and PEG-IFN 180 groups are significantly greater than that in IFN 3 MIU group ($P<0.025$).

The sustained virological, sustained biochemical, and histological response rates in PEG-IFN 180 are also significantly greater than those in IFN 3 MIU group (all $P<0.025$).

The sustained virological and sustained biochemical response rates in PEG-IFN 135 group are also significantly greater than those in IFN 3 MIU group ($P<0.025$).

In contrast to study NV15495, the results in Table 2 show that there is no clear evidence of dose response relationship in this study.

Table 2. Study NV15496: Combined Sustained Biochemical and Virological Response at Week 72, Virological Response at Week 72, Biochemical Response at Week 72, and Histological Response at Week 72.

Response	Arm A IFN 3 MIU N=214 (%)	Arm B PEG-IFN 135 µg N=215 (%)	Arm C PEG-IFN 180 µg N=210 (%)	Odds Ratio (97.5% CI) A vs. B	Odds Ratio (97.5% CI) A vs. C
Sustained Response at Week 72					
Combined Virological and Biochemical	9	20	20	2.5 (1.3, 4.8) P=0.001	2.4 (1.2, 4.8) P=0. 003
Virological	9	22	22	2.8 (1.5, 5.3) P=0.001	3.0 (1.5, 5.8) P=0.001
Biochemical	13	22	23	1.9 (1.0, 3.4) P=0.018	1.9 (1.1, 3.5) P=0.012
Histological* (all patients)	31	38	44	1.4 (0.9, 2.1) P=0.129	1.8 (1.2, 3.0) P=0.004
Histological (in patients with paired biopsies#)	45	48	58	1.1 (0.6, 1.7) P=0.820	1.8 (1.0, 3.0) P=0.017

P-values are from Cochran-Mantel-Haenszel test stratified by center

* Histological response = decrease of at least 2 points in HAI score; patients without a liver biopsy at the end of untreated follow-up are defined as nonresponders.

Patients with paired biopsies: N=147 in IFN 3 MIU; N=171 in PEG-IFN 90 µg; N=160 in PEG-IFN 180 µg.

III. Study NV15497

1. Design

This Phase III study was a randomized, *open-label*, and multicenter (36 centers from Europe, South America, Canada, Australia, and Asia) trial evaluating the safety and efficacy of PEG-IFN 180 µg and IFN in patients diagnosed with chronic hepatitis C. A total of 531patients were randomized to receive either PEG-IFN 180 µg sc once a week for 48 weeks or IFN sc tiw, 6 MIU for 12 weeks then 3 MIU for 36 weeks. Patients were treated for 48 weeks and then followed for additional 24 weeks. Randomization was centralized and was stratified by center.

The primary efficacy parameter was a combined sustained virological and sustained biochemical response at the end of the 24 week untreated follow-up period. This rate was calculated as the number of patients with both a sustained biochemical and virological response divided by the number of patients randomized.

The Secondary efficacy endpoints were sustained virological response at the end of follow-up, sustained biochemical response at the end of follow-up, and histological response in all patients and in patients with paired biopsies.

This study was designed to demonstrate that the combined sustained virological and biochemical response with PEG-IFN is no worse, by more than 5%, than the combined sustained response rate with IFN. This test of equivalence was then to be followed by a test of superiority to demonstrate that the combined sustained response with PEG-IFN was superior to that with IFN.

2. Results

The results on the primary and secondary efficacy parameters are given in Table 3.

The combined sustained virological and biochemical response rate in PEG-IFN 180 µg group is significantly greater than that in IFN 6/3 MIU group ($P<0.001$).

The sustained virological and sustained biochemical response rates in PEG-IFN 180 µg group are also significantly greater than those in IFN 6/3 MIU group (all $P<0.001$).

The sustained histological response rates in PEG-IFN 180 µg group are also greater than those in the IFN 6/3 MIU group. However, they are not statistically significant (Table 3).

Table 3. Study NV15497: Combined Sustained Biochemical and Virological Response at Week 72, Virological Response at Week 72, Biochemical Response at Week 72, and Histological Response at Week 72.

Response	Arm A IFN 6/3 MIU N=264 (%)	Arm B PEG-IFN 180 µg N=267 (%)	Odds Ratio (95% CI) A vs. B
Sustained Response at Week 72			
Combined Virological and Biochemical	15	28	2.2 (1.4, 3.3) P=0.001
Virological	17	31	2.2 (1.5, 3.4) P=0.001
Biochemical	19	31	2.0 (1.3, 3.0) P=0.001
Histological* (all patients)	35	43	1.5 (1.0, 2.2) P=0.038
Histological (in patients with paired biopsies#)	55	63	1.3 (0.8, 2.1) P=0.223

P-values are from Cochran-Mantel-Haenszel test stratified by center

* Histological response = decrease of at least 2 points in HAI score; patients without a liver biopsy at the end of untreated follow-up are defined as nonresponders.

Patients with paired biopsies: N=167 in IFN 6/3 MIU; N=184 in PEG-IFN 180 µg.

Conclusion

The results from these three pivotal trials show that the sustained virological and biochemical response rate in patients treated with PEG-IFN is significantly greater than that in IFN-treated patients.

The sustained virological and sustained biochemical response rates in PEG-IFN 180 are also significantly greater than those PEG-IFN-treated patents.

There is some evidence that histological response shows greater improvement in patients treated with PEG-IFN as compared with patients treated with IFN. However, these improvements are not always statistically significant.